Ataxia and Weakness in a Young Woman

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A 28-year-old woman presented with slowly progressive ataxia and signs of upper and lower motor neuron dysfunction. She had no family history of neurologic disease. Neuroimaging study results were unremarkable, and the diagnosis remained obscure for several years. The differential diagnosis of motor system degeneration in a young adult is broad but focuses on inherited disorders that may have late onset. In this case, close analysis of the clinical features in the history and neurologic examination and interpretation of the laboratory study results led to the diagnosis.

REPORT OF A CASE

A 28-year-old woman presented with motor incoordination and lower-extremity weakness progressing slowly for 2 years. She reported a “drunken” gait and slurred speech. In addition, she experienced difficulty climbing stairs and getting up from low-seated positions. She also reported frequent calf cramps and muscle twitching. She had no visual symptoms and no sensory, bladder, or bowel issues.

She had had bipolar disorder with manic and depressive episodes since 14 years of age. Her medical history was otherwise unremarkable for any contributing factors. She reported no travel history and no known human immunodeficiency virus or toxin exposure. She lived with her father and assisted with the family business. Her father was of Pennsylvania Dutch Amish descent. Her mother was of Northern European ancestry and died at the age of 54 years of complications from alcoholism. She had no siblings. There was no family history of neurologic disorders.

Mental status was normal during the clinical interview. Pupillary light reflexes and funduscopic examination findings were normal. Square wave jerks, symmetrical saccades, and saccadic pursuit were observed, but otherwise extraocular movements were intact. She had no weakness or fasciculations of bulbar muscles. She exhibited marked weakness of bilateral hip flexors and knee extensors (greater on the left than the right). The upper extremities and distal lower extremities were strong. Fasciculations were prominent throughout both lower extremities. Reflexes were diffusely brisk with bilateral Hoffmann signs and a hyperactive jaw jerk. She had no clonus. Plantar responses were equivocal. Truncal, speech, and heel-shin ataxia was present without upper limb ataxia. Her gait was both ataxic and waddling (consistent with proximal leg weakness). Sensory examination findings were normal.

INITIAL DIAGNOSTIC STUDIES

Hemogram, blood electrolyte levels, and liver function test results were normal. Serum angiotensin-converting enzyme, vitamin B12, vitamin E, thyroid-stimulating hormone, ceruloplasmin, and serum protein electrophoresis levels were normal. The results of tests for antinuclear antibody, human immunodeficiency virus, rapid plasma reagin, antigliadin IgG and IgA, paraneoplastic antibody, anti–glutamic acid decarboxylase antibody, urine heavy metal, and a complete genetic ataxia panel (including analysis for spinocerebellar ataxia [SCA] types 1, 2, 3, 5, 6, 7, 10, 12, 13, 14, 17, and 28 and frataxin) were all negative or normal. Leukocyte arylsulfatase A (ARSA) activity was decreased at 2.4 U (reference range, >2.5 U). The creatine kinase level was mildly elevated at 219 U/L (to convert to microkatal per liter, multiply by 0.0167).

Motor and sensory nerve conduction studies of all 4 limbs were normal. Electromyography revealed fasciculations, positive sharp waves, fibrillations, and large, poorly recruited motor units in the left gastrocnemius, anterior tibialis, and vastus medialis muscles. The results of electromyography of the upper limb and paraspinal muscles were normal. Brain magnetic resonance
imaging (MRI) (Figure 1) revealed cerebellar atrophy. The cerebral white matter and brainstem were normal.

**CLINICAL DISCUSSION**

The patient’s history and examination implicate a pathologic process that affects the cerebellum, pyramidal tracts, and anterior horn cells or ventral nerve roots. When evaluating a progressive, multifocal neurologic disorder that affects motor neurons and the cerebellum, degenerative, inherited, metabolic, and inflammatory disorders need to be considered. Given the onset in a young adult, inherited disorders should receive the most attention.

Laboratory study results were largely normal. The ARSA enzyme deficiency in leukocytes suggests the diagnosis of metachromatic leukodystrophy. Although this patient’s ARSA enzyme activity level was decreased, the diagnosis of metachromatic leukodystrophy is improbable in the absence of an abnormal white matter signal on brain MRI. Instead, the laboratory abnormality likely represents ARSA pseudodeficiency, which is found in 5% to 20% of the healthy population and is due to genetic polymorphisms, resulting in lower than average ARSA leukocyte activity without any clinical manifestations.

The SCAs are a genetically diverse group of multisystem, neurodegenerative disorders whose common feature is progressive ataxia. Most autosomal dominant forms of SCA are caused by expansion of trinucleotide repeats. SCA2, SCA3, and rarely SCA6 have been reported to cause both ataxia and clinical features resembling amyotrophic lateral sclerosis (ALS). Groote Eylandt motor neuron disease, a disease initially described among Australian Aborigines characterized by spasticity, ataxia, weakness, and amyotrophy, was later found to be due to SCA3 mutation.1 Interestingly, intermediate-length polyglutamine expansion in ataxin 2, the protein responsible for the manifestations of SCA2, is linked to an increased risk for ALS.2 Although SCA with motor neuron disease would explain the clinical presentation in this case, the lack of SCA mutations (specifically SCA2, SCA3, and SCA6) makes this a less likely diagnosis. Also, most SCAs are autosomal dominant, and this patient has no family history.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay, first described in the 1970s in Quebec, Canada, is characterized by progressive spastic paresis and ataxia with a slowly progressive sensorimotor polyneuropathy (axonal and demyelinating). Neuro-ophthalmic findings include myelinated and thickened retinal nerve fiber layer, jerk nystagmus, impaired smooth pursuit, impaired optokinetic nystagmus, and saccadic dysmetria.3 Brain MRI demonstrates characteristic linear pontine T2 hypointensities and cerebellar vermis and cervical cord atrophy.4 Funduscopic examination and brain MRI in our patient did not reveal these unique findings, making this diagnosis unlikely.

The GM2 gangliosidoses are rare autosomal recessive disorders due to a deficiency in lysosomal hexosaminidase (HEX). Deficiency of HEX A causes Tay-Sachs disease, and deficiency of both HEX A and B causes Sandhoff disease. These 2 diseases lead to accumulation of gangliosides in the brain and spinal neurons and are almost indistinguishable phenotypically.5 There are 3 variants distinguished by age of onset (infantile, juvenile, and adult). Typical symptoms include neuropsychiatric manifestations, including intellectual impairment, pyramidal tract signs, sphincteric disturbances, cerebellar ataxia, and extrapyramidal signs.5 Both Tay-Sachs disease and Sandhoff disease have been reported to present with a clinical picture of motor neuron disease that resembles ALS.6,7 Interestingly, saccadic abnormalities have been noted in GM2 gangliosidoses, including hypometria, intrasaccadic decelerations, premature saccadic termination, and abnormalities of saccadic latency.8 The presence of psychiatric disease, saccadic abnormalities, cerebellar ataxia, and lower motor neuron manifestations makes adult-onset GM2 gangliosidosis a likely diagnosis. Although the carrier incidence in the general population is approximately 1 in 250, the incidence among Ashkenazi Jews and French Canadians is 1 in 30. This patient is at risk because genetic susceptibility is also higher among those of Pennsylvania Dutch and Northern European and Irish descent.
Sporadic neurodegenerative disorders, such as multiple system atrophy, can be considered as well. Multiple system atrophy is a progressive disorder associated with glial cytoplasmic inclusions of α-synuclein characterized by autonomic failure, ataxia, and parkinsonism. There have been rare reports of multiple system atrophy coexisting with motor neuron disease.9 Multiple system atrophy with motor neuron disease is an unlikely diagnosis in our patient given her young age and the absence of any autonomic manifestations or parkinsonian features.

A number of unusual infectious or inflammatory diseases with protean neurologic manifestations should be considered, including Whipple disease, Erdheim-Chester disease, and neurosarcoïdosis. Whipple disease (caused by intestinal infection with Tropheryma whipplei) leads to various neurologic manifestations, including cerebellar ataxia, pyramidal tract signs, and, in rare cases, peripheral neuropathy.10 The pathognomonic clinical feature, oculomasticatory myorhythmia, was not present in this patient. Furthermore, the lack of constitutional symptoms, rheumatic symptoms, ocular signs, and alimentary tract symptoms makes this diagnosis less likely.

Erdheim-Chester disease typically occurs in older patients and is characterized by systemic infiltrates of non-Langerhans histiocytes. Neurologic manifestations occur in a third of patients. Although any part of the central nervous system may be involved, lesions typically affect the hypothalamic-pituitary axis (causing diabetes insipidus), cerebellum, and pons (leading to ataxia and pyramidal tract dysfunction). Again, although possible, the likelihood of Erdheim-Chester disease is remote, in view of the lack of endocrine or systemic manifestations.

Neurosarcoïdosis can result in variable neurologic manifestations (most commonly cranial neuropathies or myelitis) that may precede the appearance of systemic signs. Rare reports have been made of coexisting ALS and neurosarcoidosis.11 A normal serum angiotensin-converting enzyme level does not exclude neurosarcoidosis; even cerebrospinal fluid angiotensin-converting enzyme levels are of little diagnostic use. Although the lack of typical clinical and neuroimaging features makes this diagnosis less likely, chest computed tomography and cerebrospinal fluid examination would help evaluate this possibility further.

Superficial siderosis results from hemosiderin deposition in central nervous system areas adjacent to cerebrospinal fluid and exhibits a predilection for the superior cerebellar vermis, cerebellar folia, basal frontal lobe, temporal cortex, brainstem, spinal cord, nerve roots, and cranial nerves I and VIII. There is almost always a history of trauma, intradural cranial surgery, or the presence of a tumor or previously ruptured aneurysm or arteriovenous malformation. It usually manifests with progressive cerebellar ataxia, deafness, vestibulopathy, ophthalmic dysfunction, and pyramidal signs. Neurocognitive deficits are late findings. There are reports of superficial siderosis mimicking ALS due to deposition of hemosiderin in the ventral nerve roots.12

In this patient, however, the clinical course had been more rapid than expected for superficial siderosis, and she did not have clinical evidence of deafness or vestibulopathy. Further neuroimaging, including susceptibility weighted MRI studies, would be useful to demonstrate hemosiderin deposition along the surface of the cerebellum, spinal cord, cisternal portion of the cranial nerves (especially cranial nerve VIII), and spinal roots.
Other entities to be considered include ataxia with oculomotor apraxia type 2 (mutations in senataxin have also been associated with familial ALS type 4) and familial coenzyme Q10 deficiency (associated with cerebellar atrophy and neuropathy).

### NEUROPATHOLOGIC DISCUSSION

Additional laboratory studies revealed a leukocyte HEX A activity level of 9% (reference range, >63% of control activity). Levels associated with symptomatic GM2 gangliosidosis are typically less than 15%, with infantile cases having activity levels of less than 5%. Levels in carriers are approximately 40%. Low levels may be seen in asymptomatic patients who have benign variants that reduce the ability of HEX A to interact with the synthetic test substrate but do not interfere with activity in vivo. Enzyme activity may be tested in serum or leukocytes. Leukocyte testing is preferred for women who are pregnant or taking oral contraceptives because serum levels of HEX may be falsely reduced.

Genetic testing demonstrated compound heterozygosity in the HEXA gene (OMIM 6006809) on chromosome 15 (Figure 2). One mutation, G269S, was a missense mutation in exon 7, leading to an amino acid substitution (serine for glycine) and resulting in reduced levels of the α-subunit and defective association with the β-chain. This is the most common mutation in patients with adult-onset disease. The second mutation, IVS 9 (+1), substitutes adenine for guanine at the donor splice site in intron (intervening sequence) 9, leading to abnormal splicing and undetectable messenger RNA. It is a common mutation in the Pennsylvania Dutch population, as well as in French, Cajun, Scottish, Irish, and Welsh populations. At the latest follow-up (age of 32 years), 6 years after symptom onset, the patient had worsened and required a cane or walker for mobility and was experiencing dysphagia for thin liquids.

### CONCLUSIONS

The final diagnosis was adult-onset Tay-Sachs disease (GM2 gangliosidosis). This case illustrates several principles regarding adult-onset inherited and metabolic diseases of the nervous system. First, onset can be at any age rather than only during early development. For unknown reasons, pathogenic enzyme deficiencies can remain asymptomatic during much of the life span. Whether this is due to metabolic pathway redundancies that become inefficient later in life, accumulation of a toxic product, saturation of a detoxifying cellular system, or activation of secondary pathogenic mechanisms remains virtually unexplored. Second, both disease manifestations and disease course are age specific and not necessarily stereotyped. For example, the retinal cherry-red spot, startle myoclonus, and thalamic MRI T2-prolongation typical of infantile GM2 gangliosidosis are not characteristic of the adult-onset form, which causes prominent neuropsychiatric manifestations, giving rise, in fact, to a distinct syndrome. In this patient, the early history of bipolar disease is entirely consistent with the diagnosis.

Third, despite widespread deficiency of crucial enzymatic activities, neurometabolic disorders are universally regional diseases, preferentially affecting specific cells or neural elements while sparing others. Although certain mutations are commonly associated with clinical disease (such as the HEXA G269S mutation in Tay-Sachs), incompletely penetrant forms, genetic mosaicism, and phenocopies are common occurrences in neurometabolic disorders. Enzymatic testing, although an inaccurate predictor of disease severity or phenotype, is often the only effective means to establish an antemortem diagnosis in progressive multifocal adult neurologic disorders.

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